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Publication number: **0 192 460 B1**

(12)

## EUROPEAN PATENT SPECIFICATION

(43) Date of publication of patent specification: 21.08.91 (51) Int. Cl.<sup>5</sup>: A61K 9/20, A61K 9/68

(21) Application number: 86301125.0

(22) Date of filing: 18.02.86

(54) Quick-liquifying chewable tablet.

(30) Priority: 19.02.85 US 702818

(43) Date of publication of application:  
27.08.86 Bulletin 86/35

(45) Publication of the grant of the patent:  
21.08.91 Bulletin 91/34

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:  
EP-A- 0 049 143 EP-A- 0 089 280  
EP-A- 0 124 663 DE-A- 2 643 121  
FR-A- 2 364 059 GB-A- 736 591  
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EP 0 192 460 B1

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## Description

The present invention relates generally to tablets which quickly liquify upon being broken and subjected to a liquid, particularly to tablets which quickly liquify in the mouth when chewed, and to processes for their manufacture.

A need has long existed in the pharmaceutical industry for an oral dosage form which stores well, is convenient and pleasant to take, efficacious, fast acting, and portable. Liquids are desirable because the active ingredients are already liquified, they can be swallowed easily, and, in the case of preparations such as antacids and cough medicines, soothe the throat and oesophagus on the way to the stomach. However, liquids are not easily portable, often require refrigeration and require some utensil to measure and administer the dosage. Solid dosage forms, such as tablets, usually are portable and easily stored, but a liquid such as water is usually required as an aid in swallowing, and they are generally not as fast acting or as efficacious as liquids. While some tablets, such as antacid tablets, can be chewed to begin dissolution which is completed in the stomach, they do not liquify in the mouth and are swallowed as gritty particles.

Antacid preparations are sold in both liquid and solid form to treat a wide range of disorders such as simple upset stomach, heartburn, acid or nervous indigestion and ulcers. Liquids, while being generally preferred because they are perceived to be faster acting and better tasting, and because they react more quickly with excess gastric acid and immediately soothe oesophageal heartburn or nervous indigestion, suffer from the previously mentioned drawbacks. Currently available solid antacid tablets are quite portable and convenient to take, but do not liquify well in the mouth, are not perceived to be as effective as the liquids and do not soothe esophageal heartburn or nervous indigestion on the way to the stomach. Moreover, solid antacid tablets are not particularly good tasting and do not sweeten the breath, which would be extremely desirable for those who suffer from oesophageal reflux or sour breath. In addition, solid antacid tablets when chewed produce gritty and chalky particles which are unpleasant tasting and quite unpalatable.

EP-A-089280 discloses compression in one direction of a mixture of neutral excipients and an active substance in the form of granules so that the integrity of the granules is not damaged; but the products are capsules, not tablets.

US 4327077 relates to soft-chewable tablets comprising particles of recrystallized fatty material and an antacid, and a carbohydrate, e.g. various sugars, which binds the particles in to tablets after compression at 400 to 1000psi.

GB 736591 says that in which processes of compacting powdered material the particles are not uniformly pressed together and some particles may be deformed and others left loosely with spaces. A new fluidized compaction method e.g. for detergents or food stuffs is provided; tablets are not disclosed.

US 3305447 discloses sugar (sucrose) tablets with a binder, e.g. of invert sugar, and an active ingredient, e.g. phenobarbital.

It is an object of the present invention to provide a tablet which stores well and liquifies quickly when used, particularly a tablet which liquifies quickly in the mouth upon chewing and is pleasant tasting.

It is another object of the present invention to provide a tablet by direct compression, which includes a substantial quantity of an active ingredient, particularly an active ingredient which in its raw material form is a powder that can not be compacted into a cohesive tablet easily or at all.

According to the present invention we provide a chewable tablet which comprises particles of

- (a) at least 25 wt % of an agglomerate, of bulk density 0.2 to 0.5 g/cc, composed of 90 to 99 wt % of particles of size less than 300 $\mu$ m of a carbohydrate and 1 to 10 wt % of a water-soluble binder and
- (b) up to 75 wt % of an active ingredient dispersed in the agglomerate,

the tablet having a hard outer shell formed by compressing the particles to a hardness of 59 to 176 N (6 to 18 kp) and the tablet being rapidly liquifiable when the shell is broken and the softer interior of the tablet is then contacted with a liquid.

A tablet according to the present invention is thus directly compressed from specially formed high surface area, carbohydrate-based agglomerate particles and comprises a relatively soft, quick-liquifying interior and a relatively hard, protective outer shell which resists liquification even though it is formed from the same agglomerate particles which form the tablet interior. At least some of the ingredients of the agglomerate particles in the interior of the tablet quickly dissolve or partially dissolve when contacted with small amounts of a liquid, particularly water and/or saliva, and any remaining ingredients which do not dissolve in the liquid become dispersed in the liquid and dissolved ingredients, so that the resulting liquid is smooth and essentially without perceivable grit.

The agglomerate particles which form the tablet interior are rapidly liquified when the tablet is broken up, as for example during mastication, and the particles are contacted with small amounts of a liquid including, for example, the saliva normally available in the mouth. However, the relatively hard outer shell

resists liquification until it is broken, for example by chewing. Accordingly, the overall tablet structure is such that the tablet is not only stable and easily portable, thereby providing a unit dose in the most convenient form, but is also readily liquified and melts in the saliva of the mouth during mastication without requiring water or some other liquid, so that the tablet provides all of the benefits normally associated only with liquid dosage forms.

The carbohydrate particles can be selected from dextrose, dextrose monohydrate, maltodextrin, fructose, sucrose, lactose, maltose and xylose; and the water-soluble binder can be selected from maltodextrin, corn syrup solids, dextrose, sucrose, polyvinyl pyrrolidone and cooked starch paste. The proportion by weight in the agglomerate (without active ingredient) of water-soluble binder is critical and must be in the range of from 1 to 10 percent, preferably from 1 to 5 percent, with the carbohydrate particles comprising from 90 percent to 99, preferably 95 to 99 percent.

While not wishing to be limited to any particular theory, it is believed that the agglomerates from which the tablets are made have an open pore or duct-like structure and a resulting large surface area to volume ratio which causes the particles to readily dissolve on contact with small amounts of any liquid, including saliva, in which the agglomerate is at least partially soluble. The pores or ducts of the agglomerate structure which are believed to provide the large surface area are capable of entraining relatively large quantities of an active ingredient. The agglomerate structure is thus honeycomb in nature and resembles that of zeolite. By virtue of this structure, the large surface area of the agglomerate becomes accessible for contact by a liquid in which at least the carbohydrate binder dissolves so that the agglomerate particles quickly liquify and entrain or dissolve the active ingredient depending on its solubility. This agglomerate structure is believed not to be substantially destroyed in the interior of the tablet by compression, while the relatively hard outer shell of the tablet, although made from the same material as the interior of the tablet, appears to be formed from partial destruction or blockage of the agglomerate pore structure at the tablet surface as a result of the compressive forces which are applied by the smooth walls of the mold cavity during formation of the tablet. The shell thus acts as a protective mechanism which not only mechanically assists in holding the tablet together but also blocks the open pore structure in the interior of the tablet from the exterior of the tablet and thereby inhibits penetration of a liquid solvent into the interior of the tablet. It was quite surprising and unexpected to find that the agglomerates could be subjected to a pressure sufficient to cause the agglomerate particles to adhere and form a mechanically stable tablet which included a relatively hard outer shell, and yet retain the quick-liquifying characteristics of the agglomerate in the interior of the tablet.

The term "active ingredient" is used herein in a broad sense and encompasses any material which can be carried by or entrained in the agglomerate. For example, an active ingredient can be a pharmaceutical such as an antacid, analgesic or drug; or a flavor, breath sweetener, vitamin, dietary supplement, or nutrient; or the like and combinations thereof. Active ingredients include food acids; insoluble metal and mineral hydroxides, carbonates, oxides, polycarbophils and salts thereof; adsorbates of active drugs on a magnesium trisilicate base and on a magnesium aluminum silicate base.

The agglomerate can be formed from the carbohydrate particles and the water-soluble binder without an active ingredient, and the active ingredient and agglomerate can be mixed to cause the active ingredient to be entrained by and dispersed in the agglomerate. The agglomerate used (without the active ingredient) has a bulk density of from 40 percent to 55 percent of the bulk density of the carbohydrate-based particles before they are processed into the agglomerate. The bulk density of the agglomerate itself is relatively low and in the range of from 0.2 g/cc to 0.5 g/cc (12.5 lbs/ft<sup>3</sup> to 31.2 lbs/ft<sup>3</sup>). A substantial part of the agglomerate consists of voids, i.e., pores or ducts, which provide an extremely large surface area capable of entraining and dispersing substantial quantities of active ingredients, ordinarily 10 percent to 50 percent by weight of the finished agglomerate (which includes the entrained active ingredient). The agglomerate and entrained active ingredient have particular utility as a direct compression agglomerate from which tablets according to the invention can be made, particularly chewable tablets which liquify in saliva.

A process for making the carbohydrate-based agglomerate comprises the steps of forming a fluidized bed of the carbohydrate particles, intermittently spraying a solution of the water-soluble binder in a droplet size of from 20  $\mu$ m to 100  $\mu$ m into the fluidized bed so as to cause intimate co-mingling of solution and carbohydrate particles and adhesion together of carbohydrate particles to form agglomerated particles, drying the particles in the fluidized bed between intermittent sprayings, and continuing spraying and drying until the desired amount of solution has been sprayed into the bed. Thereafter, the agglomerated particles are dried to a desired moisture content or the equilibrium moisture content. The amount of liquid binder solution sprayed corresponds to a binder content in the agglomerate of from 1 percent to 10 percent by weight of the agglomerate (excluding active ingredient). The carbohydrate-based agglomerate, and an active ingredient are mixed, preferably in a low shear blender, in the following proportion by weight of the finished

agglomerate (including active ingredient): agglomerate, 50 percent to 90 per cent; active ingredient, from 10 per cent to 50 per cent. A lubricant is also mixed together with the agglomerate and the active ingredient in the proportion of from 0.4 per cent to 1 percent by weight of the finished agglomerate (including active ingredient). Flavors can also be mixed with the agglomerate and active ingredient.

5 The agglomerate can, as formed, entrain the active ingredient and other materials such as a lubricant and flavors. In addition, an agglomerate including the entrained active ingredient can be formed by the process described above for the agglomerate formed without an active ingredient, except the active ingredient is mixed with the carbohydrate particles and a fluidized bed is formed of this mixture. When the agglomerate is formed with an entrained active ingredient, the active ingredient can comprise up to 75  
10 percent of the weight of the finished agglomerate (including active ingredient). Physical evidence shows that agglomerate formed with an active ingredient have a structure similar to that of agglomerate formed without an active ingredient.

The particle size of the materials used to make the agglomerates and the tablet have been found to be important, as described below.

15 It has been determined that tablets made from carbohydrate particles passing 50 mesh (particle size less than 300  $\mu\text{m}$ ) and water-insoluble active ingredients passing 300 mesh (particle size less than 50  $\mu\text{m}$ ) liquify quickly and melt in the mouth without perceivable grit upon chewing. (Mesh sizes given herein refer to the U.S. Standard Sieve Series.) Tablets having carbohydrate particle and water-insoluble active ingredient particle sizes greater than 300  $\mu\text{m}$  and 50  $\mu\text{m}$ , respectively, liquify too slowly in the mouth to  
20 provide a quick liquifying, melt-away tablet. Active ingredients can have a particle size larger than 50  $\mu\text{m}$  if they are water-soluble, although smaller particle sizes are desired. It has also been determined that to facilitate processing by automatic equipment the agglomerate particles should pass 22 mesh (particle size less than 80  $\mu\text{m}$ ) and be retained on 100 mesh (particle size greater than 150  $\mu\text{m}$ ).

A process for making a tablet from the finished carbohydrate-based agglomerates described above  
25 including from 0.4 percent to 1.0 percent of a lubricant, comprises compressing the agglomerate particles with entrained active ingredient and lubricant in conventional tablet-forming apparatus to a hardness sufficient to hold the tablet together and substantially destroy the open pore structure of the agglomerate at the surface of the tablet while substantially maintaining the open pore, i.e., large surface area, structure of the agglomerate in the interior of the tablet. Thus, the agglomerate is compressed so that the interior of the  
30 tablet retains the essential porous structure and other physical characteristics of the agglomerate which enable it to liquify quickly, while the physical characteristics of the agglomerate are changed primarily at the surface of the tablet.

For the materials described herein, it has been found that tablets compressed to a hardness of from 59N (6 kp) to 176N (18 kp) have an interior which essentially retains the physical structure of the  
35 agglomerate. A thinner outer shell is preferred since more force is required to break a tablet with a thicker shell and less material is provided in the interior of a tablet having a thicker shell. Since the thickness of the outer shell has been found to increase with tablet hardness, a preferred range for compression of the agglomerate is to a hardness of from 59 to 137 N (6 to 14 kp). Tablets compressed to a hardness in the range of 59 to 98 N (6 to 10 kp) have been found to have an outer shell believed to be of  $\mu\text{m}$  thickness  
40 which is sufficient to close off the interior open pore structure of the tablet, and thereby inhibit penetration of liquid through the outer shell into the interior of the tablet, and yet thick enough to provide mechanical strength to the tablet to resist breaking during manufacture and shipping. A tablet compressed to a hardness of from 59 to 137 N (6 to 14 kp) requires little force to crack, and once the tablet is broken into pieces upon chewing, liquifies rapidly in the saliva of the mouth. Tablets compressed at a hardness of from  
45 137 to 176 N (14 to 18 kp) were found to have interiors in which the agglomerate substantially retained its physical characteristics, but the shell thickness was such that the tablet as a whole was hard and not as easy to chew as were tablets compressed to hardnesses of less than 137N (14 kp). In addition, at hardnesses of from 137N (14 kp) to 176N (18 kp), the shell thickness was such that there was perceptively less material in the interior of the tablet with the desirable quick-liquifying characteristics.

50 Pressures applied to compress the agglomerates into tablets having a hardness of from 59N 6 kp to 176N 18 kp were found to be in the order of about one-third the pressures ordinarily used to make tablets.

#### Brief Description of the Drawings

55 FIG. 1 is a schematic diagram of a fluidized bed spray agglomerator which can be used in accordance with the present invention to form agglomerates according to the present invention;  
FIG. 2 is an enlarged schematic diagram of a spray nozzle used in the apparatus of FIG. 1 to inject liquid binder solution into the apparatus.

The invention is broadly applicable to making a wide variety of tablets including antacid tablets, cough medicine tablets, sor throat tablets, breath freshener tablets, vitamin tablets, calcium tablets, dietary supplement and nutrient tablets, laxative tablets, cold tablets, analgesic tablets, anti-diarrhea tablets, reducing tablets, pain reliever tablets, sleeping tablets, and many prescription and non-prescription drug and pharmaceutical tablets.

Agglomerates according to the invention can be formed by a fluidized bed/agglomeration process in which the particles to be agglomerated are maintained in a gaseous suspension, and binder in a fine spray is applied to the suspended particles to cause them to adhere together and build into agglomerated particles having the open pore, large surface area structure described herein. The suspended carbohydrate particles from which the agglomerates are made of size less than 300  $\mu\text{m}$  (passing 50 mesh), while water-insoluble active ingredients and lubricants are fine powders, for example, less than 50  $\mu\text{m}$  (passing 300 mesh). Other ingredients such as flavors are of size less than 150  $\mu\text{m}$  (passing 100 mesh). It was found convenient to use commercially available micropulverized powders (-325 mesh, less than 44  $\mu\text{m}$  particle size) for active ingredients such as calcium carbonate and a lubricant such as magnesium stearate. Where desired, these materials were screened to smaller particle sizes.

The binder is applied in a mist-like or atomized spray having a droplet size of from 20  $\mu\text{m}$  to 100  $\mu\text{m}$  in diameter. The spray is applied intermittently and the bed particles are dried between sprayings while they are continuously maintained suspended and in a fluidized state. Intermittent spraying and drying continues until the required amount of binder solution has been sprayed into the bed. The moisture content of the bed is thereafter reduced, preferably directly to the final desired moisture content or the equilibrium moisture content, and the agglomerated particles are removed from the bed and sized.

A spray granulator suitable for making agglomerates of the invention is a Freund Model FL80 pilot-production flow coater. A schematic diagram of the Freund Model FL80 flow coater is depicted in FIG. 1 and designated by reference number 10. The flow coater 10 includes a gas intake section 12, a frusto-conical body 14 into which gas from the intake section 12 is drawn to suspend particles 16 therein in a fluidized bed, and an exhaust section 18 for exhausting the gas used to fluidize the bed particles 16. Three binary-type nozzles 20 are equally-spaced about the circumference of an upper cylindrical portion 22 of the body 14, and spray binder solution into the bed particles 16. The binary nozzles 20 utilize gas flows for atomizing the binder solution and for controlling the geometric pattern of the spray.

It is preferred that air be used as the gas for atomizing the binder solution ("atomizing air"), as the gas for controlling the pattern of the spray ("spray pattern air"), and as the gas for suspending and fluidizing the particles 16 in body 14 ("fluidizing air"). Further description of the flow coater 10 will be made with respect to use of air as these gases, although it should be understood that gases other than air can be used and that for certain gases it may be desirable or necessary to use a closed loop system in which the gas is recycled, or scrubbed before release to the atmosphere.

The gas intake section 12 includes a gas inlet 24 communicated with the atmosphere through which air is drawn into the flow coater 10. Disposed in the gas intake section 12 are heat exchangers 26 through which the incoming air is forced before being introduced into a plenum 28 connected to the conical bottom portion 30 of the flow coater body 14. The heat exchangers 26 can be conventional, and steam/air heat exchangers are preferred. The fluidizing air, after suspending and fluidizing the bed particles 16, is drawn through a micron filter 32 disposed in the exhaust section 18. An exhaust blower (not shown) is communicated with the exhaust outlet 34 of section 18 to draw air through the gas intake section 12, the plenum 28 and the body 14. The entire flow coater 10 is grounded by grounding connectors 35.

The conical bottom portion 30 is a removable bowl having a bottom 36 which supports the particles 16 to be agglomerated while permitting the passage of air therethrough. The bottom 36 can comprise a screen sandwich or other structure capable of supporting powdered material while permitting air to flow through it and lift the powdered material. The bowl 30 includes an opening 38 closed by a transparent cover 40 to permit viewing into the bowl while agglomeration is proceeding.

The binary nozzles 20 are disposed in the cylindrical portion 22 of the body 14 equally spaced about the circumference thereof. The axes 42 of the binary nozzles 20 are disposed at an angle with the horizontal such that the axes intersect at a point generally along the central axis 44 of the body 14 at or below the nozzles. The nozzles 20 are preferably aligned so that the spray ejected therefrom strikes the rising particles perpendicularly. The spherical body portion 46 of the nozzles 20 permits the nozzles to be adjusted and aligned along desired axes in the cylindrical portion 22 of the flow coater body.

Referring to FIG. 2, each binary nozzle 20 includes openings 60, 62 and 64 through which liquid binder, atomizing air and pattern air are respectively expressed from the nozzle. A plurality of openings 62 for the atomizing air are disposed on each side of opening 60 including an annular opening surrounding opening 60, while a single opening 64 for the pattern air is provided on each side of opening 60. Passage 66

through which the liquid binder is delivered to opening 60 projects from the binary nozzle 20. The atomizing air and pattern air are expressed from the binary nozzle through a cap 68 which is threaded to the body 46 of the binary nozzle 20 and is adjustable thereon with respect to the position of the pattern air openings 64. The atomizing air and pattern air are introduced into the binary nozzle 20 through input openings 70, 71, respectively, and are communicated with regulators 72, 73, respectively, via passages 74, 75 respectively. The atomizing air and pattern air are delivered to openings 62, 64 from the regulators 72, 73 through passages 76, 77 respectively, extending through the body 46 of the nozzle 20 to the cap 68. Passage 66 for the liquid binder solution is connected via input opening 78 to a fine-toothed, relatively pulseless gear pump 79 which pumps liquid binder solution from a tank 80 to input opening 78 at a constant, pulseless rate, and recycles the solution to the tank 80 from output opening 81 when spraying is discontinued. Input openings 70 and 71 are connected with an air compressor 83 via respective air pressure valves 85, 86, to control the volume of air to output openings 62, 64, respectively. Such valves may form part of the nozzle 20. The pressure and flow rate of the air expressed through openings 62 controls atomization and particle size of the liquid binder solution expressed from opening 60, and the pressure and flow rate of the air expressed through openings 64 control the pattern of the atomized liquid binder solution. The direction of the spray pattern can be controlled by adjustment of the pattern air pressure and/or flow rate, and the atomized particle size can be controlled by adjustment of the atomizing air pressure and flow rate, and the liquid binder pump rate.

The nozzles 20 are commercially available as part of the Freund Model FL80 flow coater, and the construction and operation of the nozzles is understood by those of skill in the art.

The air pressure of the atomizing air and pattern air and the pumping rate of the liquid binder solution are set and controlled in accordance with the particular agglomerate being produced. Also controlled are the quantity of fluidizing air being drawn to fluidize the bed particles, and the heat exchangers 26 to set the temperature of the air introduced into the flow coater.

In operation, the bowl 30 charged with particles to be agglomerated is secured to the body 14 and the exhaust blower is activated to cause air to enter the inlet 14, pass through the heat exchangers 26 and enter into the body 14 after passing through the bowl 30. The incoming air lifts the particles 16 from the bowl and carries them upwardly into the central cylindrical portion 22 of the body 14 with some of the particles rising even higher into the exhaust section where they are trapped by the micron filter 32. A negative pressure is created in the body 14 and the lift created by the exhaust blower is controlled by the volume of air introduced so that the particles are lifted and maintained suspended in a fluidized state in the cylindrical portion 22, and the particles fall along the periphery of the body to be lifted again by the rising air. The particles are thus lifted and suspended and fall, continuously. After the particle motion has reached a somewhat dynamic state of fluidization, the binary nozzles 20 are activated to spray binder solution onto the fluidized particles. The axes of the nozzles are positioned and the geometric spray pattern selected so that the upper part of the composite spray of the three nozzles is located at about the middle of the cylindrical portion 22 and strikes the rising particles perpendicularly. The individual spray patterns are preferably generally fan-like in shape and the width of the individual spray patterns are such that substantially all of the cylindrical portion below and adjacent to the spray nozzles are covered by spray droplets.

The spray nozzles 20 are activated intermittently to spray the fluidized particles 16 with binder solution and the particles are maintained in a fluidized state to effect partial drying of the particles between intermittent sprayings. The micron filter 32 is periodically shaken to return particles it has trapped back to the body 14. After the desired amount of solution has been sprayed by the nozzles 20, the particles are dried to a desired moisture content after which fluidization is stopped and the agglomerated particles fall into the bowl 30 which is removed from the flow coater. The agglomerate particles are then sized when they are to be used to make tablets.

For the materials disclosed herein and similar materials, the atomizing air pressure and the pattern air pressure can be in the general range of 152 - 608 MPa (1.5 atm - 6 atm) the atomizing air flow in the general range of from 100 m<sup>3</sup>/h to 200 m<sup>3</sup>/h, the pattern air flow in the general range of from 10 m<sup>3</sup>/h to 40 m<sup>3</sup>/h, and the liquid binder flow rate in the general range of from 60 ml/min to 1,200 ml/min. The following are preferred: atomizing air pressure and pattern air pressure, 405 - 506 MPa (4-5 atm); atomizing air flow, 170 m<sup>3</sup>/h; pattern air flow, 20 m<sup>3</sup>/h; liquid binder flow rate 300 ml/min; air pressure within the flow coater, -0.5 atm; fluidizing air temperature, about 80°.

The different process parameters described above can be set and individually controlled by visual observation and manual setting, or by control systems which semi-automatically or automatically sense and regulate the parameters in accordance with a given control sequence. Process parameters for a particular agglomerate can be programmed into or manually set into such control systems. Computerized control systems can be used, if desired, and the construction and operation of control systems for controlling the

foregoing process is within the skill of those in the computer and control system arts.

Apparatus other than the Freund FL80 flow coater can be used to produce agglomerates according to the invention. One such apparatus is commercially available as a Freund mini-flow coater. This apparatus includes a single, centrally-disposed nozzle which sprays atomized binder solution into a fluidized bed from above the bed.

Agglomerates have been made in accordance with the process described above using a Freund Model FL80 flow coater. The agglomerates were made from a liquid binder solution and carbohydrate particles of the following materials: dextrose monohydrate; dextrose monohydrate and maltodextrin; fructose; fructose and maltodextrin; sucrose; sucrose and maltodextrin; lactose; lactose and maltodextrin; maltose; maltose and maltodextrin; xylose; xylose and maltodextrin. Aqueous solutions of the following materials were used as the liquid binder solution: corn syrup solids; dextrose; sucrose; polyvinylpyrrolidone; cooked starch paste; and combinations of the foregoing, any of which may also include maltodextrin. The maltodextrin binder material has a DE of less than 20% and preferably in the range of from 5% to 12%.

The carbohydrate particles passed 50 mesh (particle size less than 300  $\mu\text{m}$ ), and the water-insoluble active ingredients passed 325 mesh (particle size less than 44  $\mu\text{m}$ ). Lubricant particles passed 325 mesh and other materials such as flavors passed 100 mesh. The precise size of the carbohydrate particles is not critical, but agglomerates made from materials having sizes larger than 50 mesh for the carbohydrate particles and larger than 300 mesh for the active ingredient do not produce tablets which liquify and melt in the mouth as quickly and as completely as those made with smaller particles. Active ingredients which do not dissolve in the liquid in which a tablet made from the agglomerate is to liquify, e.g., water or saliva, preferably have a particle size of less than 10  $\mu\text{m}$ . A preferred particle size for such active ingredients is from 3  $\mu\text{m}$  to 10  $\mu\text{m}$ . Before being compressed into tablets, the agglomerate particles are sized -22 mesh, +100 mesh (between 150  $\mu\text{m}$  and 800  $\mu\text{m}$ ). The agglomerate particle size is also not critical and particles in the above range produce tablets having preferred characteristics.

Agglomerates made in accordance with the invention have a honeycomb or zeolite-like structure as described above, in which there are large amounts of voids and surface area. This structure is evident from the following physical characteristics of the agglomerates:

1. The processed agglomerate is free-flowing while the unprocessed carbohydrates generally are not.
2. The processed agglomerates remain free-flowing and do not "lump" in high humidity (e.g., 80%-85% relative humidity), while the unprocessed carbohydrates generally lump and become "mushy".
3. The processed agglomerates liquify in water completely within about 30 seconds with minimal stirring whereas the unprocessed carbohydrates resist liquification and tend to lump even when stirred.
4. The agglomerates processed without an active ingredient can entrain substantial quantities of active ingredients and liquify as described in paragraph 3 above.
5. Agglomerates processed without an active ingredient can absorb up to 25% of the weight of the agglomerate of a low viscosity oil (e.g., mineral oils having a viscosity of about 0.5 Pa·S (500 cps)) without appearing to be wet and while remaining free flowing.
6. Agglomerates processed without an active ingredient have a bulk density of from 40% to 55% of the unprocessed carbohydrate particles, and have a low bulk density of from 0.2 g/cc to 0.5 g/cc.
7. The agglomerates as viewed under a microscope had a physical structure similar to that of zeolite and are honeycomb in nature, having pores or ducts which were capable of entraining other materials.

Tablets made in accordance with the invention were found to be hard and smooth on the outside but rough, granular and soft on the inside, normally resistant to moisture on the outside and liquid-reactive on the inside. When masticated, the tablets liquified without perceivable grit within about 10 seconds.

Specific Examples of agglomerates and tablets made from the agglomerates in accordance with the invention follow. Such Examples are intended to be exemplary.

In all of the Examples which include maltodextrin, the maltodextrin was Maltrin M-100 (-100 mesh).

In Examples I-XII, the compressed air was supplied to the binary nozzles at about room temperature (e.g., 20-25°C), and the binder solution was supplied to the binary nozzles at about room temperature. The temperature of the particles charged in the flow coater (which may be at room temperature) was brought up to the bed temperature specified in the Examples by the fluidized air. The pressure in the flow coat r in Examples I-XII was about -0.5 atmospheres. The agglomerates were dried to the specified moisture content, although they can be dried to the equilibrium moisture content if desired.

EXAMPLE I

5	Agglomerate Composition	Dextrose Monohydrate	98.2% w/w
		Maltodextrin	1.8% w/w
10	Agglomerate Moisture Content	7.5%	
	Agglomerate Density	25 lbs. per cubic foot	(0.4 g/cc)
15	Agglomerate Particle Distribution	Through 22 mesh...100%	
		Retained on 88 mesh...100%	
20	Equipment	The Freund Model FL80 pre-production flow coater equipped with three adjustable, periphally mounted, binary spray nozzles as depicted in FIG. 1. Each nozzle produces a spray	
25			
		mist in a solid, fan-like configuration and is adjusted to inject the liquid binder solution generally perpendicular to the rising bed particles.	
30			
	Charge Load	55 kg Dextrose Monohydrate passing	
35		60 mesh	
	Liquid Binder	10 liters of 10% w/w maltodextrin water solution	
40	Binder Spray Rate	300 ml/minute	
	Atomizing Air Flow Rate	170 m <sup>3</sup> /h	
45	Atomizing Air Pressure	4 atmospheres	
	Pattern Air Pressure	4 atmospheres	
50			
	Fluidizing air temperature from heat exchangers	80° C	

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The agglomerat is made as follows. Charge the flow coater with the dextrose monohydrate; b gin fluidization and raise the bed temperature to 35° C. Begin spraying, with intermittent filter shaking and drying, until 10 liters of solution has been delivered through the nozzles onto the bed. Spraying is



discontinuous, i.e., spraying followed by drying followed by spraying, to obtain low density particles and to maintain the bed in dynamic motion. To this end, spraying is controlled to prevent overwetting, which could disrupt the bed dynamics and/or produce higher density particles. Dry the product to a moisture content of 7.5% and remove the dextrose monohydrate/maltodextrin agglomerate from the flow coater. Pass the dextrose monohydrate/maltodextrin agglomerates through a Sweeco sieve bank and crop particles from -22 mesh to +88 mesh.

#### EXAMPLES II - XII

The agglomerate produced according to Examples II-XII in Table A below, were made as generally described in connection with Example I. In Example II, the pressure of the atomizing air and the pattern air was 506 MPa (5 atmospheres). In Examples III-XII, the pressure of the atomizing air and the pattern air was 405 MPa (4 atmospheres). In Examples II-XII: the liquid binder flow rate was 300 ml/min.; the fluidizing air temperature was 80° C; the agglomerate density was 0.4 g/cc; and the agglomerate particle distribution was sized to -22 mesh, + 88 mesh.

## AGGLOMERATE

TABLE A

## CHARGE

## SPRAY

EXAMPLE	Composition (w/w)	Moisture Content	Particles	Binder (Liters of 10% w/w Maltodex- trin in Water)	Atom- izing Air Flow Rate $M^3/h$	Pattern Air Flow Rate $M^3/h$
II	Dextrose Monohydrate 95% Maltodextrin 5%	7.5%	Dextrose Monohydrate (-60 mesh) 52.2 kg Maltodex- trin 2.3 kg	5	170	20
III	Fructose 95% Maltodex- trin 5%	0.75%	Fructose (-100 mesh) 52.2 kg Maltodex- trin 2.3 kg	5	150	20
IV	Fructose 98.2% Maltodex- trin 1.8%	0.5%	Fructose (-100 mesh) 55 kg	10	170	20
V	Sucrose 98.2% Maltodex- trin 1.8%	0.5%	Sucrose (-100 mesh) 55 kg	10	170	20

TABLE A

EXAMPLE	AGGLOMERATE		CHARGE		SPRAY	
	Composition (w/w)	Moisture Content	Particles	Binder (liters of 10% w/w Maltodex- trin in water)	Atom- izing Air Flow Rate M <sup>3</sup> /h	Pattern Air Flow Rate M <sup>3</sup> /h
VI	Sucrose 95% Maltodex- trin 5%	0.75%	Sucrose (-100 mesh) 52.2 kg Maltodex- trin 2.3 kg	5	150	20
VII	Lactose 98.2% Maltodex- trin 1.8%	0.5%	Lactose (-100 mesh) 55 kg	10	170	20
VIII	Lactose 95% Maltodex- trin 5%	0.75%	Lactose (-100 mesh) 52.2 kg Maltodex- trin 2.3 kg	5	150	20
IX	Maltose 98.2% Maltodex- trin 1.8%	0.5%	Maltose (-100 mesh) 55 kg	10	170	20

AGGLOMERATE		TABLE A		CHARGE		SPRAY	
EXAMPLE	Composition (w/w)	Moisture Content	Particles	Binder (Liters of 10% w/w Maltodex- trin in water)	Atom- izing Air Flow Rate M <sup>3</sup> /h.	Pattern Air Flow Rate M <sup>3</sup> /h.	
X	Maltose 95% Maltodex- trin 5%	0.75%	Maltose (-100 mesh) 52.2 kg Maltodex- trine 2.3 kg	5	150	20	
XI	Xylose 98.2% Maltodex- trin 1.8%	0.5%	Xylose (-100 mesh) 55 kg	10	170	20	
XII	Xylose 95% Maltodex- trin 5%	0.75%	Xylose (-100 mesh) 52.2 kg Maltodex- trin 2.3 kg	5	150	20	

The agglomerates of Examples I-XII exhibited the quick-liquifying characteristics described herein and were suitable for making the inventive tablets described herein. The agglomerates exhibited good flow characteristics, did not lump in high humidity, liquified in water within 30 seconds with minimal stirring and were capable of entraining up to 50% by weight of an active ingredient.

EXAMPLE XIII

In Example XIII, a direct compression agglomerate including an active ingredient was processed directly, as generally described for Example I. The process parameters were as follows:

5

	Atomizing air pressure	405 MPa (4 atm)
	Pattern air pressure	405 MPa (4 atm)
10	Atomizing air flow rate	170 M <sup>3</sup> /h
	Pattern air flow rate	20 M <sup>3</sup> /h
	Liquid binder flow rate	30 ml/min.
	Fluidizing air temperature	80° C
15	Binder solution	10 liters of 10% w/w maltodextrin in water

The particles were dried to a moisture content of 4.0% and screened -22 mesh, +88 mesh.

20 In XIII A-C, the charge was 60 kg and in XVII D and E, the charge was 300 g. In XIII A-D, the flavors, the citric acid and the magnesium stearate, were added after the agglomerate was formed. The particle size of the calcium carbonate was 3  $\mu$ m to 10  $\mu$ m. The magnesium stearate passed -325 mesh and the flavors passed -100 mesh.

25

	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>E</u>	
	<u>% w/w</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>	
30	Calcium Carbonate	25.00	49.00	40.00	76.6	52.00
	Dextrose (-50 mesh)	71.25	48.50	57.00	22.2	43.90
	Maltodextrin	2.54	1.29	2.79	---	1.09
	Maltodextrin	1.21	1.21	1.21	2.2	1.21
	as 10% Aqueous Solution					
35	Flavors	0.20	0.20	0.20	0.20	0.36
	Citric Acid	1.00	1.00	1.00	1.00	1.00
	Matnesium Stearate	0.60	0.60	0.60	0.60	0.50

40 The agglomerates of Example XIII were observed to have generally the characteristics of the agglomerates of Examples I-XII except that they entrained up to about 76.6% by weight of an active ingredient.

EXAMPLES XIV - XVIII

45 In Examples XIV through XVIII, the specified active ingredient and lubricants and flavors such as citric acid were milled and weighed, and the specified agglomerate was weighed. These raw materials were then charged, in the pre-weighed quantities falling within the range of 10% to 50% by weight of the active ingredient and additives and from 50% to 90% by weight of the carbohydrate-based agglomerate, into a low shear blender, e.g., a low intensity ribbon-type mixer or a double trough sigma-type low intensity mixer. The raw materials were mixed in the low shear blender until the active and other ingredients were substantially entrained within the agglomerate. The resulting or finished agglomerate was discharged from the mixer and after validation was ready to be compressed into tablets. The aluminum hydroxide gel and the calcium carbonate had a particle size of from 3  $\mu$ m to 10  $\mu$ m while the dextromethophan adsorbate passed 100 mesh. The magnesium stearate passed 325 mesh and the flavors passed 100 mesh.

55

EXAMPLE XIV

	(a)	(b)
5 Dried Aluminum Hydroxide gel (w/w)	25.0%	50.0%
Magnesium Stearate (w/w)	0.7%	0.7%
Flavors (w/w)	0.3%	0.3%
10 Example I Agglomerate (w/w)	74.0%	49.0%

EXAMPLE XV

	(a)	(b)
15 Magnesium Carbonate (w/w)	25.0%	50.0%
Magnesium Stearate (w/w)	0.7%	0.7%
20 Flavors (w/w)	0.3%	0.3%
Example II Agglomerate (w/w)	74.0%	49.0%

EXAMPLE XVI

	(a)	(b)
25 Dried Aluminum Hydroxide gel (w/w)	10.0%	15.0%
30 Magnesium Carbonate (w/w)	10.0%	15.0%
Calcium Carbonate (w/w)	10.0%	15.0%

	Magnesium Stearate (w/w)	0.7%	0.7%
	Flavors (w/w)	0.3%	0.3%
5	Example II Agglomerate (w/w)	69.0%	50.0%

EXAMPLE XVII

10		(a)	(b)
	10% Dextromethorphan HB <sub>B</sub> /		
	Magnesium Misilicate Ad <sub>B</sub> sorbate (w/w)	6.8%	16.5%
	Magnesium Stearate (w/w)	0.7%	0.7%
15	Flavors (w/w)	0.3%	0.3%
	Example III Agglomerate (w/w)	92.2%	82.2%

EXAMPLE XVIII

20		(a)	(b)
	10% Dextromethorphan HB <sub>B</sub> /		
25	Magnesium Misilicate Ad <sub>B</sub> sorbate (w/w)	6.8%	16.8%
	Magnesium Stearate (w/w)	0.7%	0.7%
	Flavors (w/w)	0.3%	0.3%
30	Example II Agglomerate (w/w)	92.2%	82.2%

The agglomerates of Examples XII-XVIII exhibited the quick-liquifying characteristics described herein and were suitable for making the inventive tablets described herein. The agglomerates exhibited good flow characteristics, did not lump in high humidity, and liquified in water at room temperature within 30 seconds with minimal stirring.

EXAMPLES XIX - XXIV

In Examples XIX through XXIV, the finished agglomerate was introduced into standard tableting apparatus and compressed at reduced pressures over those used conventionally. The pressure was selected to yield tablets having hardnesses of from 59N (6 kp) to 78N (8 kp) and from 118N (12 kp) to 137N (14 kp), which produced tablets having an outer shell in which the large surface area structure of the agglomerate was essentially destroyed and an interior which retained the open-pore structure. In each of Examples XIX through XXIV, the finished agglomerate was compressed into 1.5 g flat-faced, bevelled-edge tablets. In Examples XIX through XXIII, the calcium carbonate had a particle size of from 3  $\mu$ m to 10  $\mu$ m and the oyster shell passed 300 mesh. The magnesium sterate and citric acid passed 325 mesh. The flavors passed 100 mesh.

EXAMPLE XIX

		(a)	(b)
5	Calcium Carbonate (Food Grade) (w/w)	30.0%	50.0%
	Magnesium Stearate (w/w)	0.7%	0.7%
	Flavors (w/w)	0.3%	0.3%
10	Example II Agglomerate (w/w)	69.0%	49.0%

EXAMPLE XX

		(a)	(b)
15	Calcium Carbonate U.S.P. (w/w)	30.0%	50.0%
	Magnesium Stearate (w/w)	0.7%	0.7%
	Flavors (w/w)	0.3%	0.3%
20	Example II Agglomerate (w/w)	69.0%	49.0%

EXAMPLE XXI

		(a)	(b)
25	Calcium Carbonate (w/w)	30.0%	50.0%
	Magnesium Stearate (w/w)	0.7%	0.7%
	Flavors (w/w)	0.3%	0.3%



Example I Agglomerate (w/w)	69.0%	49.0%
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EXAMPLE XXII

	(a)	(b)
Oyster Shell (w/w)	30.0%	50.0%
Magnesium Stearate (w/w)	0.7%	0.6%
Flavors (w/w)	0.3%	0.4%

Example I Agglomerate (w/w)	69.0%	49.0%
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EXAMPLE XXIII

	(a)	(b)
Oyster Shell (w/w)	30.0%	50.0%
Magnesium Stearate (w/w)	0.7%	0.7%
Flavors (w/w)	0.3%	0.3%

Example II Agglomerate (w/w)	69.0%	49.0%
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EXAMPLE XXIV

The agglomerate of Examples XVIII A-D compressed to a tablet hardness of 69-88N (7-9 kp).

EXAMPLE XXV

(Breath Sweetener)

Calcium Carbonate (w/w)	8.0%
Magnesium Stearate (w/w)	0.6%
Flavors (w/w)	0.4%
Citric Acid (w/w)	1.0%

Example I Agglomerate	90.0%
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Tablet Hardness	59-78 N (6-8 kp)
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The tablets of Examples XIX-XXV were found to have the characteristics described herein, i.e., a relatively hard outer shell and a relatively soft interior. The outer shell resisted liquification and unbroken tablets were generally non-hygroscopic. However, once the outer shell was broken and the tablet broken into pieces, it liquified quickly in water, and when masticated, it liquified in the mouth within a few seconds to about 10 seconds into a smooth liquid without perceivable grit. The invention applies to agglomerates and tablets other than the antacids, cough medicines and breath sweetener of the Examples.

Claims

1. A chewable tablet which comprises particles of

(a) at least 25 wt % of an agglomerate, of bulk density 0.2 to 0.5 g/cc, composed of 90 to 99 wt % of particles of size less than 300  $\mu$ m of a carbohydrate and 1 to 10 wt % of a water-soluble binder and

(b) up to 75 wt % of an active ingredient dispersed in the agglomerate,

the tablet having a hard outer shell formed by compressing the particles to a hardness of 59 to

176 N (6 to 18 kp) and the tablet being rapidly liquifiable when the shell is broken and the softer interior of the tablet is then contacted with a liquid.

2. A tablet according to Claim 1 wherein said carbohydrate is selected from dextrose, dextrose monohydrate, maltodextrin, fructose, sucrose, lactose, maltose and xylose.
3. A tablet according to Claim 1 or 2, wherein the water-soluble binder is selected from maltodextrin, corn syrup solids, polyvinyl pyrrolidone and cooked starch paste.
4. A tablet according to Claim 3, wherein the binder consists of maltodextrin.
5. A tablet according to Claim 1, wherein the proportion of binder in the agglomerate is 1 - 5 wt %.
6. A tablet according to any preceding claim wherein the particle size of the agglomerate is less than 800  $\mu\text{m}$  and greater than 150  $\mu\text{m}$ .
7. A tablet according to any preceding claim wherein the particle size of the active ingredient is not more than 50  $\mu\text{m}$ .
8. A tablet according to any preceding claim, wherein the active ingredient is a food acid, water-insoluble metal or mineral hydroxide, a carbonate, oxide or polycarbophil or salt thereof or the adsorbate of an active drug on a magnesium trisilicate or magnesium aluminum silicate base.
9. A tablet according to Claim 8, wherein said active ingredient is dried aluminum hydroxide gel, magnesium carbonate, ground oyster shells, calcium polycarbophil or sodium bicarbonate.
10. A tablet according to any preceding claim, wherein the agglomerate from which the tablet is made has an open pore structure capable of entraining a large quantity of the active ingredient and having a large surface area so that the agglomerate liquifies quickly on contact with a liquid, and the compressed outer shell of the tablet has a structure in which the pores are substantially destroyed or blocked so as to inhibit penetration of a liquid into the tablet.
11. A process of making a tablet as claimed in any preceding claim, which comprises making the agglomerate by forming a fluidized bed of the carbohydrate particles, intermittently spraying a solution of the water-soluble binder in a droplet size of 20 - 100  $\mu\text{m}$  into the fluidized bed to cause co-mingling of the solution and particles and adhesion of the particles to form agglomerated particles, drying the particles between the sprayings, and continuing spraying and drying until the desired amount of the solution has been sprayed into the fluidized bed, and drying the agglomerated particles;  
and mixing the thus prepared agglomerate and a desired quantity of the active ingredient; and compressing the agglomerate in a tablet-forming apparatus to a hardness of 59 to 176 N to hold the tablet together and substantially destroy the pore structure of the agglomerate at the surface of the tablet while maintaining the open pore structure in the interior of the tablet.
12. A method as claimed in Claim 11, wherein the tablets are compressed to a hardness of the outer shell of from 59 to 137 N (6 - 14 kp).
13. A method as claimed in Claim 12, wherein the tablets are compressed to a hardness of from 59 - 98 N (6-10 kp).

#### Revendications

1. Comprimé à croquer constitué de particules de
  - (a) au moins 25% en poids d'un agglomérat, de densité apparente de 0,2 à 0,5 g/cm<sup>3</sup>, composé de 90 à 99 % en poids de particules d'un glucide de dimension particulaire inférieure à 300  $\mu\text{m}$  et de 1 à 10% en poids d'un liant hydrosoluble et
  - (b) jusqu'à 75% en poids d'un ingrédient actif dispersé dans l'agglomérat,
 le comprimé ayant une enveloppe extérieure dure formée par compression des particules à une dureté de 59 à 176 N (6 à 18 kp) et le comprimé étant rapidement liquéfiable lorsque l'enveloppe

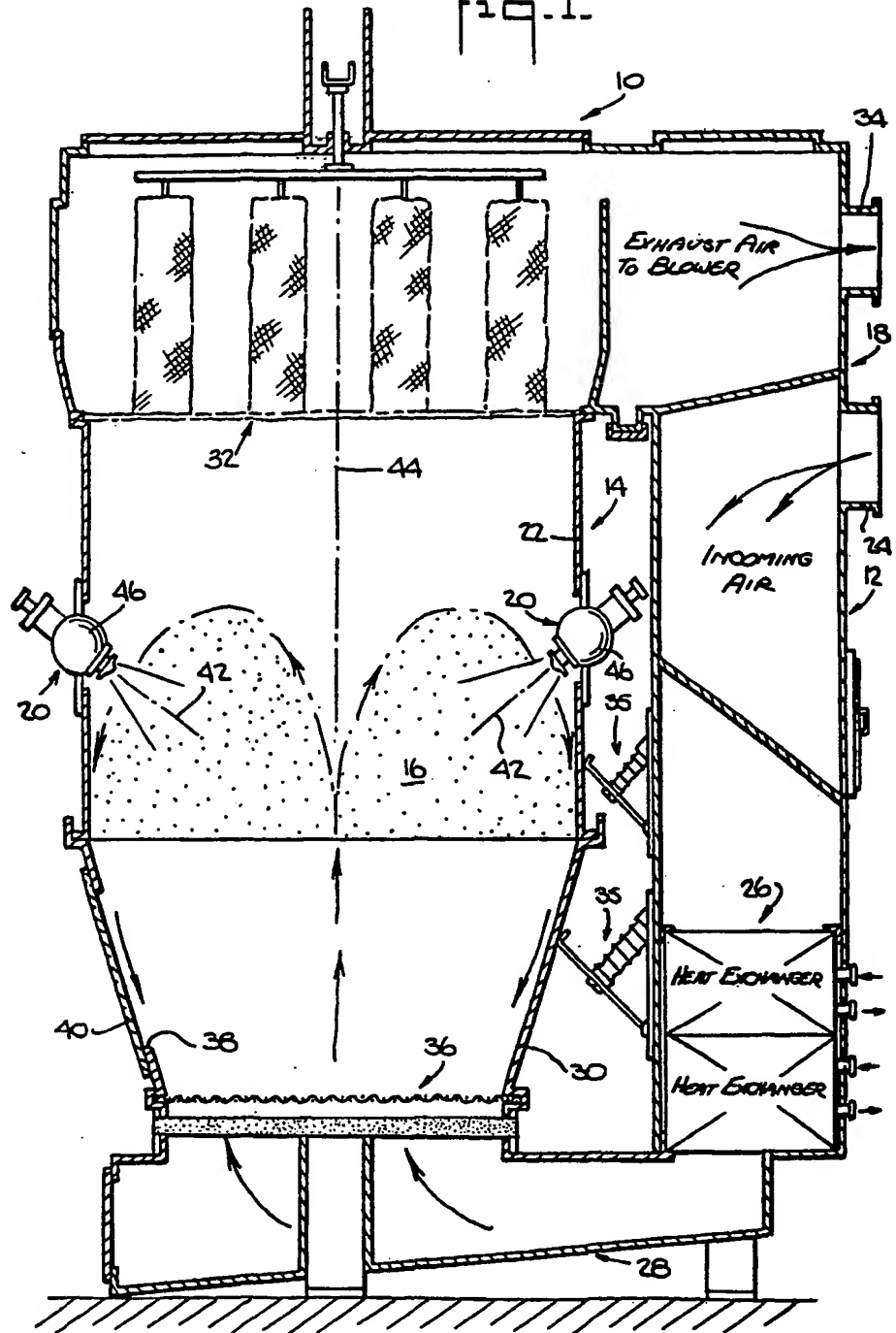
Bindemittels und

(b) bis 75 Gew.% eines in dem agglomerierten Stoff dispergierten Wirkstoffs,

wobei die Tablette eine harte Außenschale aufweist, die durch Verdichten der Teilchen auf eine Härte von 59 bis 176 N (6 bis 18 kp) gebildet wird, und die Tablette sich schnell verflüssigen läßt, wenn die Schale gebrochen wird und der weichere Inhalt der Tablette dann mit einer Flüssigkeit in Berührung kommt.

2. Eine Tablette nach Anspruch 1, bei der das besagte Kohlehydrat aus der Gruppe Dextrose, Dextrosemonohydrat, Maltodextrin, Fructose, Sucrose, Lactose, Maltose und Xylose ausgewählt wird.
3. Eine Tablette nach Anspruch 1 oder 2, bei der das wasserlösliche Bindemittel aus der Gruppe Maltodextrin, Maissirupfeststoffe, Polyvinylpyrrolidon und gekochter Stärkepasta ausgewählt wird.
4. Eine Tablette nach Anspruch 3, bei der das Bindemittel aus Maltodextrin besteht.
5. Eine Tablette nach Anspruch 1, bei der der Anteil Bindemittel in dem agglomerierten Stoff 1 - 5 Gew.% ist.
6. Eine Tablette nach einem der vorstehenden Ansprüche, bei der die Teilchengröße des agglomerierten Stoffes geringer ist als 800  $\mu\text{m}$  und größer als 150  $\mu\text{m}$ .
7. Eine Tablette nach einem der vorstehenden Ansprüche, bei der die Teilchengröße des Wirkstoffs 50  $\mu\text{m}$  nicht überschreitet.
8. Eine Tablette nach einem der vorstehenden Ansprüche, bei der der Wirkstoff eine Lebensmittelsäure, wasserunlösliches Metall oder Mineralhydroxid, ein Carbonat, Oxid oder Polycarbophil bzw. ein Salz davon oder das Adsorbat eines aktiven Arzneimittels auf einer Basis von Magnesiumtrisilicat oder Magnesiumaluminiumsilicat ist.
9. Eine Tablette nach Anspruch 8, bei der der besagte aktive Wirkstoff getrocknetes Aluminiumhydroxidgel, Magnesiumcarbonat, gemahlene Austerschalen, Calciumpolycarbophil oder Natriumbicarbonat ist.
10. Eine Tablette nach einem der vorstehenden Ansprüche, bei der der agglomerierte Stoff, aus dem die Tablette gefertigt wird, eine offene zum Mitführen einer großen Menge des Wirkstoffes fähige Porenstruktur und eine große Oberfläche hat, so daß sich der agglomerierte Stoff bei Berührung mit einer Flüssigkeit schnell verflüssigt, wobei die verdichtete Außenschale der Tablette eine Struktur aufweist, bei der die Poren im wesentlichen zerstört oder verstopft sind, so daß sie das Eindringen einer Flüssigkeit in die Tablette hemmen.
11. Ein Verfahren zur Herstellung einer Tablette nach einem der vorstehenden Ansprüche, umfassend die Fertigung des agglomerierten Stoffes durch Bilden einer Wirbelschicht der Kohlehydratteilchen, intermittierendes Einsprühen einer Lösung des wasserlöslichen Bindemittels mit einer Tröpfchengrößen von 20- 100  $\mu\text{m}$  in die Wirbelschicht, um Vermischen der Lösung und der Teilchen und Zusammenhaften der Teilchen zwecks Bildung agglomerierter Teilchen zu bewirken, Trocknen der Teilchen zwischen den Sprühvorgängen und weiteres Sprühen und Trocknen, bis die gewünschte Lösungsmenge in die Wirbelschicht eingesprüht wurde, sowie Trocknen der agglomerierten Teilchen;  
und Mischen des auf diese Weise hergestellten agglomerierten Stoffes mit einer gewünschten Menge des Wirkstoffes; und Verdichten des agglomerierten Stoffes in einem Tabletten bildenden Apparat auf eine Härte von 59 bis 176 N, um die Tablette zusammenzuhalten und die Porenstruktur des agglomerierten Stoffes an der Oberfläche der Tablette im wesentlichen zu zerstören, gleichzeitig aber die offene Porenstruktur im Inneren der Tablette zu wahren.
12. Ein Verfahren nach Anspruch 11, bei dem die Tabletten auf eine Härte der Außenschale von 59 bis 137 N (6 - 14 kp) verdichtet werden.
13. Ein Verfahren nach Anspruch 12, bei dem die Tabletten auf eine Härte von 59 - 98 N (6 - 10 kp) verdichtet werden.

Fig. 1.



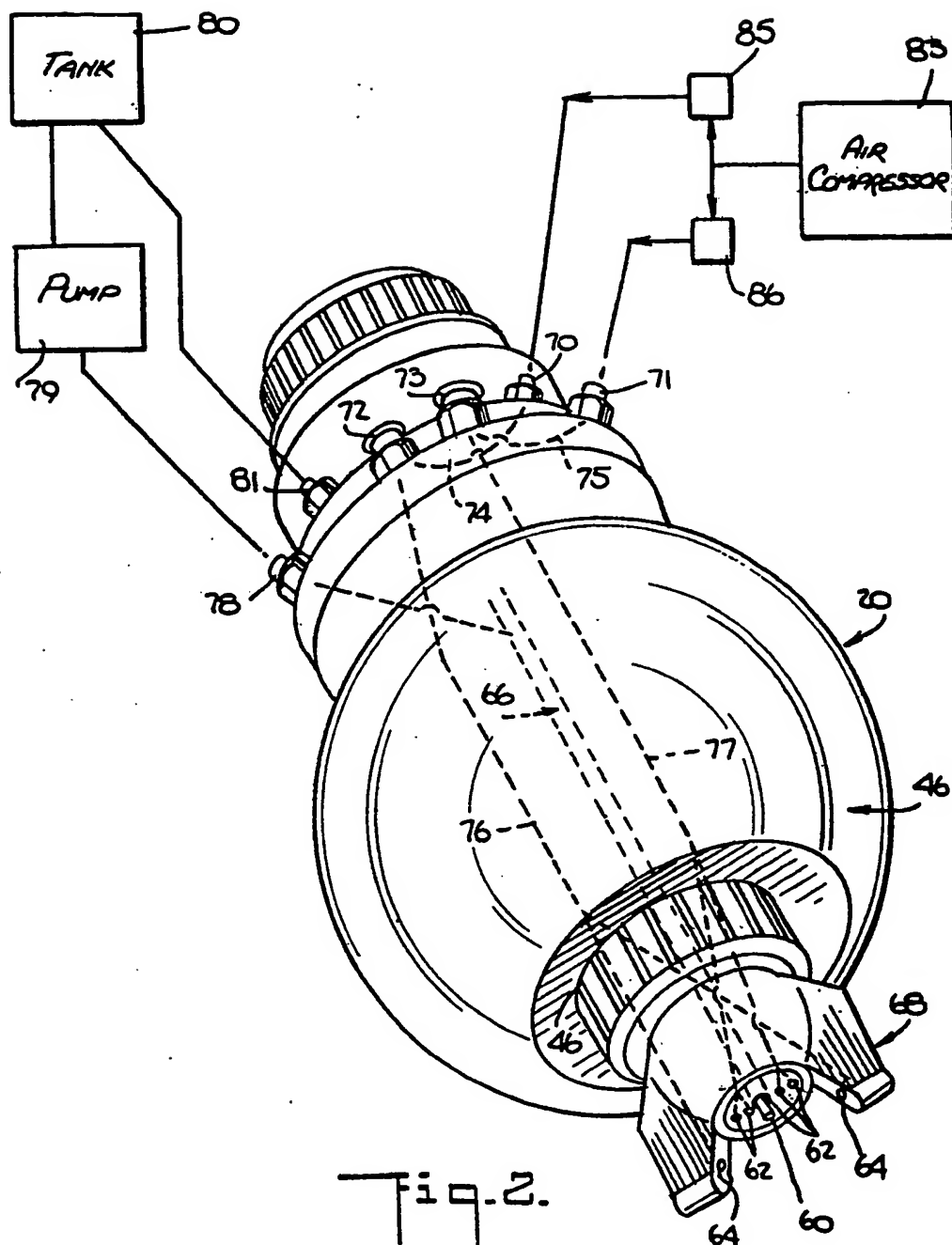


Fig. 2.